UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: August 21st, 2014

SUBJECT: **Ethoxyquin:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of June 5, 2014: Recommendation on Multiple Toxicology Studies.

PC Codes: 055501
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0053945
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

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THROUGH: Jeff Dawson, Co-Chair
Anna Lowit, Ph.D., Co-Chair
HASPOC
HED (7509P)

TO: Abdallah Khasawinah., Ph.D., Toxicologist
Kelly O'Rourke, ORE
Cropp-Kohlligian, Chemist
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Health Effects Division (7509P)

MEETING ATTENDEES

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Evans, Jeff Dawson, Jonathan Chen, Michael Metzger, P.V. Shah, Ray Kent, Jonathan Leshin, Uma Habiba, Chris Schlosser

Presenters: Abdallah Khasawinah, Ph.D.

Other Attendees: Ronnie Bever, Kelly O'Rourke

I. PURPOSE OF MEETING

The Office of Pesticide Programs is tasked with developing a human health scoping document for ethoxyquin. On date June 5, 2014, HED's Hazard and Science Policy Council (HASPOC) met to evaluate the adequacy of the toxicology database of ethoxyquin. Few guideline toxicity studies have been submitted to HED for ethoxyquin (the six pack acute battery, 28-90 day oral studies in rats and dogs); however, there is extensive published information available on ethoxyquin.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT

Ethoxyquin is an antioxidant used as a deterrent of scald in pears through a post-harvest (indoor) application via a drench, thermal fogging and/or impregnated wrap. Ethoxyquin was initially registered as a pesticide in 1965 with a Registration Standard published in 1981. Currently seven products are registered; one emulsifiable concentrate, one soluble concentrate and five impregnated materials.

One tolerance, at 40 CFR §180.178, is established for residues of ethoxyquin (1, 2-dihydro-6-ethoxy-2, 2, 4-trimethylquinoline) from postharvest use in or on pears at 3 ppm. FDA has established additional food and feed additive tolerances which are discussed below.

Due to its current use pattern (indoor use only), no exposures to water are expected.

Ethoxyquin, also has many non-pesticide uses, is a preservative in animal feed with food and feed additive tolerances published by FDA, under 21 CFR § 172.140 and a stabilizer and anti-degradation agent for rubber 21 CFR § 177.2600. Ethoxyquin has a feed additive tolerance published by FDA under 21 CFR § 573.400 in certain dehydrated forage crops, such as alfalfa, clover, grasses, and sorghum, to retard the destruction of carotene and vitamin E. Ethoxyquin is also used for stabilizing fat soluble vitamins, such as vitamins A and E, to maintain the quality of feed.

III. PHYSICAL AND CHEMICAL PROPERTIES

Ethoxyquin (MW = 217.34) is liquid at room temperature (melting point of 0° C), insoluble in water, miscible with animal and vegetable fat and oils. It has a vapor pressure of 1.82×10^{-5} mm Hg @ 0° C (purified material); 2.56×10^{-4} mm Hg @ 25° C.

IV. TOXICITY OF ETHOXYQUIN

Ethoxyquin has been the subject of numerous studies because of its wide use as an antioxidant and its role as microsomal oxidase system inducer. It has been extensively investigated along with other antioxidants for the modification of the carcinogenic properties of known carcinogens. It has been the subject of several reviews:

- the National Toxicology Program in 1990 (**NTP, 1990**): http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/ethoxyquin_508.pdf, http://ntp.niehs.nih.gov/?objectid=BD7AA2BB-123F-7908-7B625575BF384791

- JMPR (**JMPR, 1998**): http://www.inchem.org/documents/jmpr/jmpmono/v098pr09.htm
- (Blaszczyk *et al*, 2013 Int. J of Food Sciences Volume 2013, Article 585931, http://dx.doi.org/10.1155/2013/585931),
- (EFSA Journal 2013;11(5):3231 Report on ethoxyquin: 25 pages, http://www.efsa.europa.u/en/efsajournal/doc/3231.pdf)

It was nominated by the FDA NTP testing; the current status of the NTP testing is found in this link: http://ntp.niehs.nih.gov/testing/status/agents/ts-m88005.html:

- Pre-chronic dose-feed studies completed (*have not been reported*)
- Chemical disposition, metabolism, and toxicokinetics completed. (Sanders *et al* 1996 Xenobiotica 26:583-595; Burka *et al* 1996 Xenobiotica 26:597-611)
- Pilot teratology studies have been completed (*have not been reported*)

Although the published toxicology database on ethoxyquin is very extensive, OPPTS guideline studies are very limited. These are the available OPPTS guideline studies:

MRID 43885901 (1995) Acute Oral – Rats
MRID 43885902 (1995) Acute Dermal- Rats
MRID 43894101 (1996) Acute Inhalation – Rats
MRID 43885903 (1995) Primary eye Irritation – Rabbits
MRID 43885904 (1995) Primary Skin Irritation – Rabbits
MRID 43885905 (1995) Dermal Sensitization – Albino Guinea Pigs
MRID 44098901 (1996) Developmental Toxicity Study – Rats
MRID 44099001 (1996) Dose Range-Finding Developmental Toxicity Study – Rats
MRID 46338901 (2004) Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells
MRID 44123801 (1996) A 28-Day Oral (Gavage) Toxicity Study in Rats
MRID 44123901 (1996) A 90-Day Oral (Gavage) Toxicity Study in Rats
MRID 44148901 (1996) A 90-Day Oral (Capsule) Toxicity Study in Dogs
MRID 44149001 (1996) A 28-Day Oral (Capsule) Dose Range-Finding Study in Dogs
MRID 44222501 (1997) A 28-Day Oral (Gavage) Toxicity Study in Rats

Ethoxyquin has low to moderate acute toxicity by the oral (Category III), dermal (Category III) and inhalation (Category III) exposure routes. It is not an eye irritant (Category IV), and produces minimal irritation to the skin (Category IV). Tests in animals show it to have a weak sensitizing potential; however, extensive human experience from the use of this chemical showed strong association with contact dermatitis that ceased upon discontinuation of working in an ethoxyquin environment.

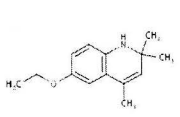
The primary target organs for ethoxyquin in experimental animals are the liver and kidney. Dogs are much more susceptible to ethoxyquin toxicity than rats with effects occurring at doses as low as 4 mg/kg/day over a 90 day feeding period. Ethoxyquin did not cause developmental effects in rats tested at doses of 350 mg/kg/day during the gestation period or in rats at doses as

high as 500 mg/kg of a 67% ethoxyquin formulation. Published studies in rats and dogs indicate that reproductive/offspring toxicity occurs at higher doses than maternal toxicity doses. Published studies do not indicate a neurotoxic concern for ethoxyquin.

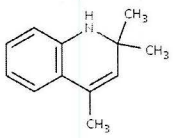
The available literature does not indicate carcinogenic potential for ethoxyquin. Published studies indicate that ethoxyquin reduces or inhibits the activity of a number of carcinogens. In mutagenicity testing, ethoxyquin is negative in *Salmonella*, negative in the micronucleus assay, negative for chromosomal aberrations and positive for *in vitro* sister chromatid exchanges in Chinese hamster ovary cells.

The only suggestion of a potential carcinogenic effect for ethoxyquin came from Manson *et al* (*1987, Ethoxyquin alone induces preneoplastic changes in rat kidney while preventing induction of such lesions in liver by aflatoxin b-1 . Carcinogenesis (London); 8 (5):723-728*) study where feeding of male Fisher 344 rats of ethoxyquin at 0.5% in the diet (5000 ppm, equivalent to 250 mg/kg/day) for 23 weeks caused severe damage to the kidneys and produced many hyperplastic and putative preneoplastic tubules.

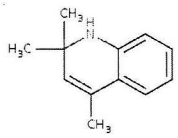
Ethoxyquin is is structurally related to flectol H_4 (1,2-dihydro-2,2,4-trimethylquinoline) and it also has toxic effects in the kidney of male rats. Flectol carcinogenicity studies were conducted by the dermal route in F344/N rats and $B6C3F_1$ mice in the National Toxicology Program *(NTP 1997. Toxicology and Carcinogenesis Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (CAS No. 147-47-7) in F344/N Rats and $B6C3F_1$ Mice and the Initiation/Promotion (Dermal Study) in Female Sencar Mice. NTP Technical Report Series No. 456).* Flectol (greater than 90% purity) was topically applied in acetone for 2 years at 0, 36, 60 or 100 mg/kg body weight, 5days/week (rats) and mice received 0, or 3.6, or 10 mg/kg body weight, 5 days/week. In mice, no neoplasms or nonneoplastic lesions were attributed to treatment with flectol. However, in rats, incidences of renal tubule adenoma and adenoma or carcinoma (combined) in all treated groups of males were significantly greater than those in the controls. The relative right kidney weights of the 60 and 100 mg/kg male rats were significantly greater than those of the controls at the 15 month sacrifice. It was concluded that "under the conditions of these 2-year dermal studies, there was some evidence of carcinogenic activity of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats, based on increased incidence of renal tubule adenoma and adenoma or carcinoma (combined). There was no evidence of carcinogenic activity of 1,2-dihydro-2,2,4-trimethylquinoline in female F344/N rats receiving 30, 60, or 100 mg/kg or in male or female $B6C3F_1$ mice receiving 3.6, 6, or 10 mg/kg."



Ethoxyquin



Flectol H



Flectol A

V. DIETARY AND OCCUPATIONAL EXPOSURE RISK ASSESSMENT

The point of departure (POD) for acute dietary exposure is 3 mg/kg based on a no-observed-adverse-effect-level (NOAEL) from a developmental rabbit study[1] . For chronic dietary exposure, dermal and inhalation exposure assessment for all durations, a POD was selected from a 90-day subchronic dog study (MRID 44148901) based on the NOAEL/LOAEL (low-observed-adverse-effect-level ; LOAEL) of 2/4 mg/kg/day based on elevated liver enzymes and microscopic findings in the liver (cytoplasmic vacuolation and minimal hepatocelular necrosis).

In the 2004 ethoxyquin risk assessment, the ethoxyquin acute and chronic (non-cancer) dietary exposure analyses assumed tolerance level residues and 100 % crop and feed treated. The dietary assessment included food exposures from pesticidal use as well as ethoxyquin's use as an antioxidant in feeds (e.g., meat, poultry and eggs) and as a food preservative (e.g., spices). Available meat/poultry cooking study data were used to reduce estimated residues in cooked livestock tissues by 96%. The overall acute dietary risk from residues in foods was 14 % of the aPAD at the 95th percentile of exposure for the females 13-49 year old sub-population. The overall chronic dietary risk from residues in foods was 5% of the chronic acute population adjusted dose (cPAD) for the average exposure of the general U.S. population and 14% of the cPAD for children 1 to 2 years of age, the most highly exposed population subgroup.

Occupational exposure scenarios include: handlers (i.e., a mixers/loaders for post-harvest treatments via automated drenching systems or thermal fogging, and mixer/loader/applicators using hand-held pressurized handguns for direct in-line spaying) as well as post-application workers (i.e., persons wrapping pears with impregnated paper, and persons sorting/packing/culling of pears following ethoxyquin treatment). The exposure estimates from the 2004 and 2008 assessments have been revised to reflect updated evaluation methodologies. Screening-level margins of exposure (MOEs) calculated in preparation for HASPOC deliberations for dermal exposure with chemical-resistant gloves range from 5.6 (direct spraying with hand-held equipment) to 590 (mixing/loading for thermal fogging). Inhalation MOEs range from 88 (sorting/packing) to 100,000 (mixing/loading for thermal fogging). The level of concern (LOC) is for the screening MOEs less than 100.

VI. HASPOC CONCLUSIONS

A very conservative risk assessment using the most conservative endpoints of toxicity (the acute endpoint was based on a study without an effect at the highest dose tested) revealed no dietary risk from the currently registered use of ethoxyquin. However, as summarized in Table 1, screening MOEs for dermal exposure with chemical-resistant gloves range from 5.6 (direct spraying with hand-held equipment) to 590 (mixing/loading for thermal fogging). Inhalation MOEs range from 88 (sorting/packing) to 100,000 (mixing/loading for thermal fogging). The LOC is for screening MOEs less than 100. Screening MOEs lower than 100 suggest that additional route-specific information would be useful in providing more accurate estimates of risk to ethoxyquin. Therefore, the HASPOC, based on a weight of the evidence approach, reproduction/fertility, developmental and chronic cancer studies **are not required** at this time. An immunotoxicity study **is also not required**, since the organ targets of toxicity are liver and kidney, and there is no indication in the literature of its potential immunotoxicity A

[1] **Isenstein RS**. 1970. Ethoxyquin in rabbit feed: study of relationship to abortion and early neonatal death Am J Vet Res 31:907-909

developmental neurotoxicity study is not required since there was no evidence of neurotoxicity or neuro pathology from the published studies and there is a rat developmental study with no effects up to the highest dose tested. Similarly, a neurotoxicity battery is not recommended. **The HASPOC is requiring**: a dermal absorption study and inhalation toxicity study. The agency suggests that the registrant discuss the protocols for both studies with HED prior to conduct of the studies.

Until which time the inhalation study is submitted and found acceptable (or alternative information is provided to reduce the uncertainty), a 10X database uncertainty factor will be retained for the inhalation route.